Lesson of the week

Fatal allopurinol hypersensitivity syndrome after treatment of asymptomatic hyperuricaemia

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Allopurinol, an analogue of hypoxanthine, which inhibits xanthine oxidase, is an effective urate lowering drug that has been the cornerstone in the treatment of hyperuricaemia and gout for decades. In most patients, the drug is well tolerated, however, about 2% of treated patients develop a skin rash. Also, an estimated 0.4%, particularly people with kidney failure or having concomitant thiazide diuretic therapy, may experience a severe idiosyncratic reaction, known as allopurinol hypersensitivity syndrome. This syndrome is characterised by skin reactions, fever, eosinophilia, and multiorgan involvement, with a mortality of 25%.[1–3]

About 5% of the population and a quarter of hospitalised patients are hyperuricaemic. Most are asymptomatic and will never develop gout. Also, high urate concentrations do not seem to cause cardiovascular disease, as was previously thought.[4] Consequently, urate lowering agents are not indicated in the treatment of asymptomatic hyperuricaemia.[4 5] We report a case of fatal allopurinol hypersensitivity syndrome after inappropriate treatment of asymptomatic hyperuricaemia.

Case report

An 80 year old man started treatment with 300 mg allopurinol a day for asymptomatic hyperuricaemia. Uric acid concentration was measured as part of a routine biochemical profile, and was 517 µmol/l. Six weeks later he developed asthenia, anorexia, fever, diarrhoea, jaundice, abdominal pain, and pruritic skin lesions. His past medical history included a duodenal ulcer, high blood pressure, and chronic renal insufficiency. He was taking omeprazole and furosemide. On examination he was feverish. We noticed hepatomegaly, jaundice, and exfoliated skin. The white cell count was 15.4 × 10^9/l, with 16% eosinophils. Creatinine concentration was 645 µmol/l, alanine aminotransferase was 328 IU/l (normal <41 IU/l), alkaline phosphatase was 6567 IU/l (normal <280 IU/l), and total bilirubin was 535 µmol/l. Prothrombin time was markedly prolonged. We detected no hepatitis B and C antibodies. Antinuclear and antimitochondrial antibodies were absent. Abdominal ultrasound and computed tomography scans were normal.

We stopped allopurinol and started him on 60 mg prednisone a day. In the next few days, his clinical condition deteriorated, with progressive liver failure and hepatic encephalopathy that finally led to death. Autopsy showed hepatic granulomas and cholestasis.

Discussion

Raised serum urate concentrations have been associated with insulin resistance, obesity, hypertension, dyslipidemia, and atherosclerotic disease. For this reason, urate lowering drugs were widely used for people with asymptomatic hyperuricaemia in the past. No compelling evidence shows, however, that hyperuricaemia causes cardiovascular disease, and using these drugs is no longer recommended.

Conversely, although risk of gouty arthritis is increased, only a minority of asymptomatic hyperuricaemic people will develop it, and prophylactic drug therapy is not warranted.[4 5] Long term uric acid lowering therapy is indicated in gout with subcutaneous tophi, frequent attacks of gouty arthritis, or urolithiasis. Uricosuric drugs are the first line for patients with decreased renal urate excretion (75% of patients with primary gout); however, allopurinol is the most prescribed drug, because of its efficacy, irrespective of the cause of the hyperuricaemia (overproduction or underexcretion) and its convenient once daily administration.[5]

Drug hypersensitivity syndrome is a severe idiosyncratic reaction associated with taking drugs. Other names are "drug rash with eosinophilia and systemic symptoms" (DRESS) and "drug induced delayed multiorgan hypersensitivity syndrome" (DIDMOHS).[6 7] The most common triggering agents are antiepileptic drugs (phenytoin, phenobarbital, and carbamazapine), sulphonamides, and allopurinol. Other drugs include minocycline, dapsone, lamotrignine, isoniazid, gold salts, and the antiretrovirals nevirapine and abacavir.[6 8] Symptoms usually begin two to six weeks after treatment starts. Patients may have diffuse skin reactions, including maculopapular rash, toxic epidermal necrolysis, erythema multiforme, and exfoliative dermatitis. Associated rash; periorbital or facial oedema; fever; lymphadenopathy; organ dysfunction; and laboratory abnormalities, including leukocytosis, eosinophilia, and raised concentrations of liver enzymes can be found.[3 6]

Allopurinol hypersensitivity syndrome has clinical peculiarities that distinguish it from hypersensitivity syndrome caused by other drugs: lymphadenopathy is generally absent and renal involvement is more common.[9] Diagnosis of drug hypersensitivity syndrome is made clinically. A high index of suspicion is necessary in patients with a history of exposure to potentially triggering drugs and a compatible clinical picture (box). Mortality from allopurinol hypersensitivity syndrome may reach 25%. The main causes of death are liver or kidney failure, sepsis, gastrointestinal bleeding, and skin exfoliation.[1] Treatment includes discontinuation of the offending drug and supportive care. The use of steroids is controversial.[2 6]

The exact mechanism for the development of allopurinol hypersensitivity syndrome is unknown; existing data support the coexistence of immunological factors, accumulation of drug metabolites, and

Inappropriate treatment of asymptomatic hyperuricaemia with allopurinol may lead to fatal hypersensitivity

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Diagnostic criteria for allopurinol hypersensitivity syndrome[1]

- A clear history of exposure to allopurinol
- Lack of exposure to another drug which may have caused a similar clinical picture
- A clinical picture including:

(1) At least two of the following major criteria:
- Worsening renal function
- Acute hepatocellular injury
- A rash, including either toxic epidermal necrolysis, erythema multiforme, or a diffuse maculopapular or exfoliative dermatitis

Or:

(2) One of the major criteria plus at least one of the following minor criteria:
- Fever
- Eosinophilia
- Leukocytosis

viral infection.[2 3 10] The pathological substrate is often a diffuse vasculitis induced by a type III hypersensitivity reaction, with formation of immune complexes that precipitate in vascular endothelium and promote an inflammatory reaction.[11] The implication of other immunological reactions, mediated by T lymphocytes or humoral responses, is less documented.[2] Accumulation of oxypurinol (the principal metabolite of allopurinol) in renal insufficiency is considered a crucial factor for the development of allopurinol hypersensitivity syndrome and may lead to tissue damage by toxic or immunological mechanisms.[2 3] The reactivation of human herpesvirus 6 infection seems to be involved in drug hypersensitivity syndrome. The exact role is unclear; the most accepted hypothesis is that CD4 T lymphocytes are activated as an immune response to drug metabolites, and in a second stage, activated T cells may reactivate a latent herpesvirus 6 infection.[10]

Therapeutic decisions have to take into account the imbalance between expected benefit and potential harm. In asymptomatic patients, therapeutic interventions must be effective in preventing complications or progression of disease, with low risk of adverse events or deterioration of quality of life. For instance, in asymptomatic hypertensive patients, the benefits of treatment, in terms of reduction in the incidence of stroke and other cardiovascular events, are clearly superior to the potential risk of treatment with drugs. In other conditions, such as asymptomatic hereditary haemochromatosis, diagnosed with genetic testing, repeated phlebotomy prevents disease progression, and is indicated when high ferritin concentrations are found, in spite of the uncomfortable and debilitating procedure.[12]

Treating asymptomatic hyperuricaemia does not have clear benefits, and our report shows the potential harm of this practice. Allopurinol hypersensitivity syndrome most often presents as a consequence of inappropriate treatment of asymptomatic hyperuricaemia.[1 2]

Another important point in treatment with drug is considering potential interactions of a new drug with other drugs or preexisting comorbidities. Allopurinol dose must be adjusted in patients with renal failure. In most of the reported cases of allopurinol hypersensitivity syndrome, patients had evidence of renal failure before starting treatment, and, in many of them, allopurinol dose was not reduced.[3] In our patient, two consecutive mistakes were made—the unnecessary prescription and the inappropriate dosage after renal failure.

Conclusion

The incidence and potentially severe consequences of allopurinol hypersensitivity syndrome could be reduced by strictly following the established indications of allopurinol treatment and adjusting the dose in chronic renal failure. Death due to inappropriate treatment of asymptomatic hyperuricaemia is clearly unacceptable.

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Endpiece

A timeless lesson

Nan-in, a Japanese master during the Meiji era (1868-1912), received a university professor who came to inquire about Zen. Nan-in served tea. He poured his visitor's cup full, and then kept pouring. The professor watched the overflow until he could restrain himself. "It is overfull. No more will go in!" "Like this cup," Nan-in said, "you are so full of your own opinions and speculations. How can I show you Zen unless you first empty your cup."

Zen flesh, Zen bones: a collection of Zen and pre-Zen writings. Compiled by Paul Reps. New York: Anchor Books, 1989

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